# Interrelationships of Maternal Serum Leptin, Body Mass Index and Gestational Age

Ming-Jie Yang*

*Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, and National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.*

**Background:** The aim of this study was to evaluate the interrelationships between maternal serum leptin level and body mass index (BMI) at different gestational ages or during the whole pregnancy.

**Methods:** A total of 374 blood samples were obtained from 114 pregnant women when they visited the prenatal clinic for registration, Down syndrome screening test, 50 g oral glucose challenge test, hepatitis B markers test, and near or at the time of delivery. Serum leptin levels were measured by immunoradiometric assay. Linear regression analysis, 1-way ANOVA and *post hoc* tests were used to analyze the data.

**Results:** Throughout the course of pregnancy, maternal serum leptin concentration was significantly correlated with gestational age ($p = 0.001$, $r = 0.179$). A good correlation was also found between gestational age and maternal serum leptin level in the second trimester ($p = 0.021$, $r = 0.158$). A significant decline in maternal serum leptin was found in the third trimester ($p = 0.011$, $r = 0.237$). There were good correlations between maternal leptin and BMI in all 3 trimesters ($p = 0.002$ in the first trimester, $p < 0.001$ in the second trimester, $p = 0.007$ in the third trimester) and through the whole pregnancy ($p < 0.001$). Maternal BMI was related to gestational age in the second trimester ($p < 0.001$) and the whole pregnancy ($p < 0.001$), but not in the first ($p = 0.404$) and third trimesters ($p = 0.053$).

**Conclusion:** Maternal serum leptin concentration was significantly related to gestational age (except in the first trimester) and BMI in the 3 trimesters and throughout pregnancy. Serum leptin concentration peaked during the early third trimester and declined significantly thereafter. Maternal BMI was related to gestational age in the second trimester and the whole pregnancy. [*J Chin Med Assoc* 2005;68(10):452–457]

**Key Words:** body mass index, gestational age, leptin

## Introduction

Leptin, the protein of the *ob* gene produced by adipocytes,[1] regulates body weight, especially the appetite, through negative feedback control on the satiety center. Maternal body mass (e.g. the product of conception, blood volume, breasts, adipose tissue, and extracellular fluid as well as other organs) changes considerably during pregnancy. Adipose tissues, including subcutaneous fat and omentum, are the main source of leptin in both nonpregnant[2] and pregnant women. During pregnancy, there is additional secretion of leptin from the placenta, as shown by the presence of leptin in the cytoplasm of syncytiotrophoblast cells.[3,4] Other than the adipose tissues and placenta, leptin can also be secreted by fetal tissue, gastric mucosa, hepatic stellate cells,[5] and mammary epithelial cells.[6] Theoretically, maternal adaptation during pregnancy makes great changes in serum leptin levels, although conflicting results have been found in studies of the placental secretion of leptin during pregnancy.[7]

Body mass index (BMI) is related to body weight as well as serum leptin in nonpregnant women.[3] Theoretically, BMI is related to maternal serum leptin due to the increase in maternal body weight that occurs with increasing gestational age (GA). However,

*Correspondence to: Dr. Ming-Jie Yang, Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, R.O.C.
E-mail: mjyang@vghtpe.gov.tw • Received: April 7, 2005 • Accepted: July 25, 2005

Masuzaki et al[3] reported conflicting results.

The relationships between maternal serum leptin and GA have been reported by Harigaya et al[8] and Gòmez et al.[9] Their studies, which focused on the later half of pregnancy only, demonstrated statistical significance between maternal serum leptin and GA. Other studies also reported changes in leptin level during pregnancy,[10–13] but only a few focused on the relationship between maternal serum leptin and the whole gestational course. This study was designed to determine the interrelationships of maternal serum leptin and BMI with GA.

## Methods

### *Study population*

Blood samples were obtained with consent from women with a normal singleton pregnancy at prenatal visits for registration, Down syndrome screening test, 50 g glucose challenge test, hepatitis B markers test, and near or at the time of delivery. Maternal blood samples were drawn during the day, when possible, to avoid the effect of diurnal changes in serum leptin concentration.[14] Serum samples were collected from blood samples spun at 4,000*g* for 10 minutes and were stored at –20°C until assay.

The expected date of delivery was calculated from the first day of the last menstrual period. When no reliable menstrual dates were available or menstrual cycles were irregular, ultrasound calculations, especially early ultrasound measurements, were used to date the pregnancy.

Maternal characteristics including height, body weight and GA at each blood test were recorded, as well as the time of delivery.

### *Leptin assay*

Serum concentrations of leptin were measured using the ACTIVE™ Human Leptin immunoradiometric assay (IRMA; Diagnostic Systems Laboratories Inc, Webster, TX, USA) in the Department of Nuclear Medicine. The procedure employs a 2-site IRMA principle described by Miles et al.[15] The IRMA is a non-competitive assay in which the analyte (recombinant human leptin) to be measured is "sandwiched" between 2 antibodies. The first antibody is immobilized to the inside walls of the tubes while the other antibody is radiolabeled ($^{125}$I-labeled anti-leptin) for detection. The analyte present in the unknowns, standards and controls is bound by both antibodies to form a sandwich complex. Unbound reagents are removed by decanting and washing the tubes. The minimal detectable concentration of leptin was 0.10 ng/mL. The intra- and inter-assay coefficients of variation were 3.7% and 5.2%, respectively.

### *Statistical analysis*

Linear regression analysis and quadratic regression analysis were used to determine the curve and the significance of differences between the data of continuous variables. One-way ANOVA and *post hoc* tests were used to analyze leptin data between groups. Statistical analysis was carried out with SPSS version 10.0 for Windows (SPSS Inc, Chicago, IL, USA), and a $p$ value of less than 0.05 was considered significant.

## Results

There were 374 blood samples obtained in this study. In the first trimester, 45 blood samples were collected. The range of maternal serum leptin was 6.82–58.59 ng/mL and showed a correlation to body weight ($p = 0.004$, $r = 0.463$) and BMI ($p = 0.002$, $r = 0.491$), but not to GA ($p = 0.552$). Correlation was also found between maternal BMI and body weight ($p < 0.001$, $r = 0.851$), but neither BMI nor body weight was related to GA ($p = 0.404$ and 0.097, respectively) (Table 1).

**Table 1.** Interrelationships of maternal serum leptin, body mass index (BMI), body weight (BW), and gestational age (GA) in the 3 trimesters and the whole pregnancy

| | First trimester | | Second trimester | | Third trimester | | Whole pregnancy | |
|---|---|---|---|---|---|---|---|---|
| | *p* | *r* | *p* | *r* | *p* | *r* | *p* | *r* |
| Leptin vs BW | 0.004 | 0.463 | < 0.001 | 0.570 | 0.007 | 0.275 | < 0.001 | 0.515 |
| Leptin vs BMI | 0.002 | 0.491 | < 0.001 | 0.598 | 0.007 | 0.274 | < 0.001 | 0.536 |
| Leptin vs GA | 0.552 | 0.091 | 0.021 | 0.158 | 0.011 | 0.237 | 0.001 | 0.179 |
| BMI vs GA | 0.404 | 0.143 | < 0.001 | 0.377 | 0.053 | 0.199 | < 0.001 | 0.515 |
| BW vs GA | 0.097 | 0.281 | < 0.001 | 0.368 | 0.039 | 0.212 | < 0.001 | 0.536 |
| BMI vs BW | < 0.001 | 0.851 | < 0.001 | 0.891 | < 0.001 | 0.877 | < 0.001 | 0.911 |

Values compared using linear regression analysis.

In the second trimester, there were 213 blood samples. The range of maternal serum leptin was 2.18–90.94 ng/mL, which not only correlated to body weight ($p < 0.001$, $r = 0.570$) and BMI ($p < 0.001$, $r = 0.598$), but also to GA ($p = 0.021$, $r = 0.158$) (Figure 1). A strong correlation was found between maternal BMI and body weight ($p < 0.001$, $r = 0.891$). Both maternal BMI and body weight were also correlated to GA (BMI, $p < 0.001$, $r = 0.377$; body weight, $p < 0.001$, $r = 0.368$) (Table 1 and Figure 2).

A total of 116 blood samples were obtained in the third trimester. The range of maternal serum leptin was 2.70–79.36 ng/mL and was correlated to both body weight ($p = 0.007$, $r = 0.275$) and BMI ($p = 0.007$, $r = 0.274$). However, maternal leptin was inversely correlated to GA ($p = 0.011$, $r = 0.237$) (Figure 3). Maternal body weight was related to BMI ($p < 0.001$, $r = 0.877$) and GA ($p = 0.039$, $r = 0.212$), but no correlation was found between maternal BMI and GA ($p = 0.053$, $r = 0.199$) (Table 1).

Throughout the pregnancy, maternal leptin level was not only related to body weight ($p < 0.001$, $r = 0.515$) and BMI ($p < 0.001$, $r = 0.536$) (Table 1), but also to GA ($p = 0.001$, $r = 0.179$) (Figure 4). In addition, the relationship between leptin and GA revealed a curve when compared by quadratic regression analysis ($p = 0.0001$, $r = 0.216$) (Figure 5). Both maternal body weight and BMI were related to GA (body weight, $p < 0.001$, $r = 0.536$; BMI, $p < 0.001$, $r = 0.515$) (Figure 6). A significant correlation was found between maternal BMI and body weight ($p < 0.001$, $r = 0.911$) (Table 1).

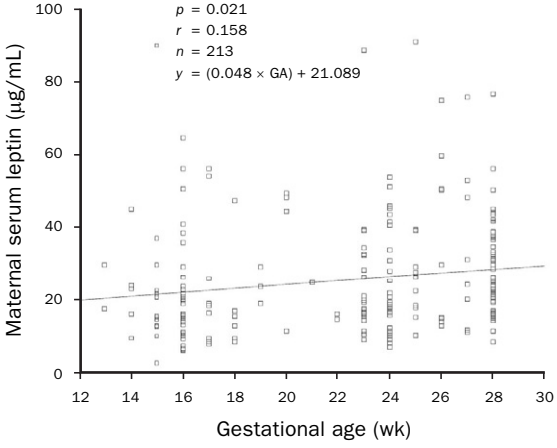


**Figure 1.** Relationship between maternal serum leptin and gestational age (GA) in the second trimester (linear regression analysis).

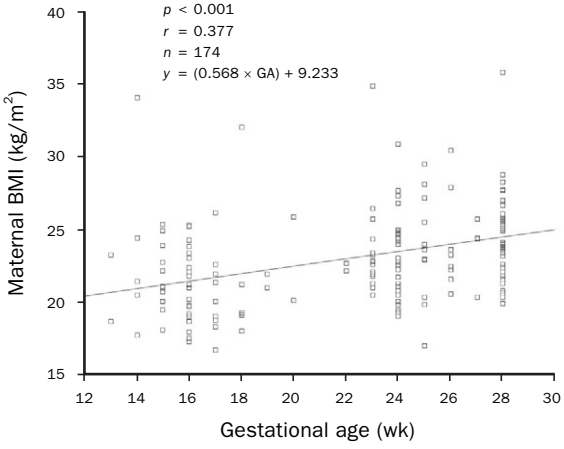


**Figure 2.** Relationship between maternal body mass index (BMI) and gestational age (GA) in the second trimester (linear regression analysis).

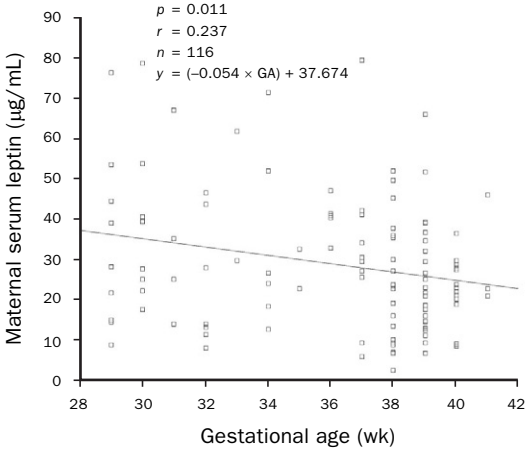


**Figure 3.** Relationship between maternal serum leptin and gestational age (GA) in the third trimester with a significant downward slope (linear regression analysis).

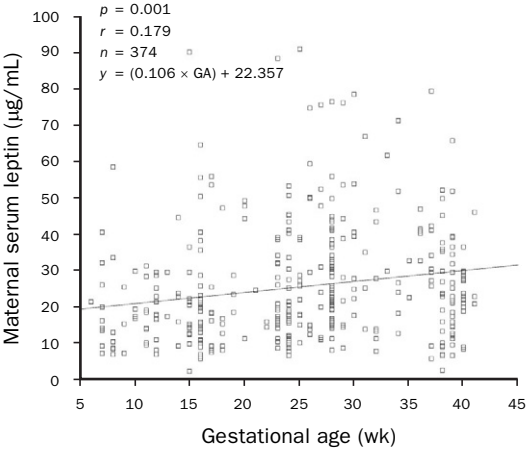


**Figure 4.** Relationship between maternal serum leptin and gestational age (GA) throughout pregnancy (linear regression analysis).

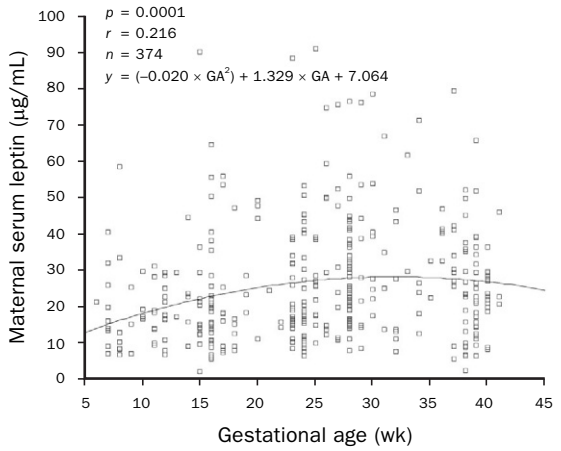


**Figure 5.** Relationship between maternal serum leptin and gestational age (GA) (quadratic regression analysis).

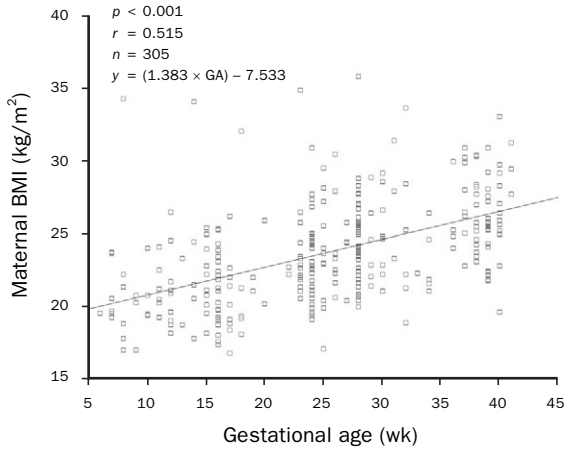


**Figure 6.** Relationship between maternal body mass index (BMI) and gestational age (GA) throughout pregnancy (linear regression analysis).

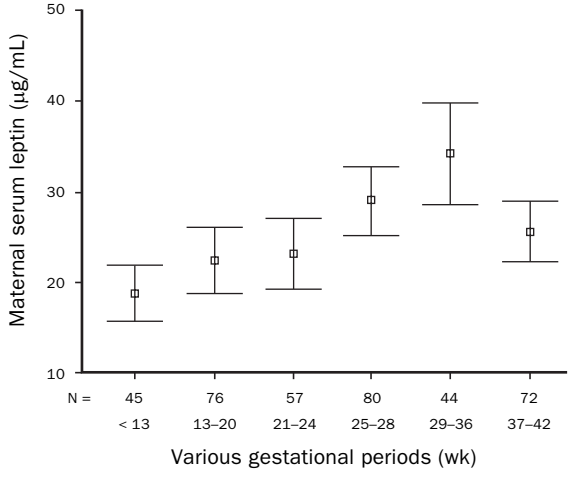


**Figure 7.** Median maternal serum leptin levels at various periods of gestation graphed with an error bar showing 95% confidence interval.

Blood samples were divided into 6 groups according to the time they were taken: less than 13, 13–20, 21–24, 25–28, 29–36, and 37–42 weeks of gestation. Leptin levels increased with GA and peaked in the early third trimester (29–36 weeks of gestation), then fell significantly in the last month of pregnancy (Figure 7). This is compatible with the fit curve for the comparison of leptin levels and GA by quadratic regression analysis (Figure 5). Significant relationships were found among leptin groups compared by 1-way ANOVA and *post hoc* tests ($p < 0.001$) (Table 2).

## Discussion

Significant correlation was found in this study between GA and maternal serum leptin levels, which was similar to the study of Tamas et al in 1998.[16] The present study, however, differs from Tamas et al's study in 3 aspects. The first difference was in sample size: in our study, 374 samples were collected from 114 pregnant women while the Tamas et al study included only 9 cases with repeated blood testing. Secondly, significant correlation was found between maternal serum leptin and GA throughout pregnancy in our study but was only found prior to the 28th week in Tamas et al's study. Thirdly, in our study, the relationships between maternal leptin and GA were evaluated separately in the 3 trimesters to reveal different significances.

Similar studies of maternal serum leptin levels during pregnancy were reported by Schubring et al,[10] Sattar et al,[11] Sivan et al,[12] and Hardie et al.[13] Blood samples were taken at skipped gestational ages in these studies where changes in maternal serum leptin levels during pregnancy were less evident. Consequently, the results were different from this study. The sample size in our study, however, was large enough to cover the whole of gestation and therefore provided a highly reliable result.

Masuzaki et al[3] and Sivan et al[12] found no correlation between maternal serum leptin and maternal BMI. In our study, however, maternal BMI was not only correlated to body weight and GA, but also related to maternal serum leptin concentration. These different results may arise from different sample sizes as well as methodology.

Nausea and vomiting are commonly seen in pregnant women during the first trimester. Although only a small portion of them gain weight, it is not uncommon for them to experience weight loss. As a result, apparent change in average body weight is rare. In this study, GA was not correlated to maternal body weight and BMI in the first trimester. Therefore, there was no significant correlation between maternal serum leptin level and GA during early pregnancy.

**Table 2.** Multiple comparisons of maternal serum leptin at various gestational ages

| GA (I) | GA (J) | Mean difference (I – J) | SE | *p* | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | Lower bound | Upper bound |
| 1 | 2 | –3.6370 | 2.9135 | 0.213 | –9.3663 | 2.0923 |
| | 3 | –4.3657 | 3.0888 | 0.158 | –10.4398 | 1.7083 |
| | 4 | –10.2244* | 2.8863 | < 0.001 | –15.9002 | –4.5486 |
| | 5 | –15.4293* | 3.2840 | < 0.001 | –21.8871 | –8.9715 |
| | 6 | –6.9180* | 2.9514 | 0.020 | –12.7218 | –1.1141 |
| 2 | 3 | –0.7287 | 2.7141 | 0.788 | –6.0658 | 4.6083 |
| | 4 | –6.5874* | 2.4811 | 0.008 | –11.4664 | –1.7084 |
| | 5 | –11.7923* | 2.9342 | < 0.001 | –17.5623 | –6.0222 |
| | 6 | –3.2810 | 2.5566 | 0.200 | –8.3084 | 1.7464 |
| 3 | 4 | –5.8587* | 2.6848 | 0.030 | –11.1383 | –0.5791 |
| | 5 | –11.0635* | 3.1084 | < 0.001 | –17.1760 | –4.9510 |
| | 6 | –2.5522 | 2.7547 | 0.355 | –7.9693 | 2.8648 |
| 4 | 5 | –5.2049 | 2.9072 | 0.074 | –10.9218 | 0.5120 |
| | 6 | 3.3064 | 2.5255 | 0.191 | –1.6599 | 8.2728 |
| 5 | 6 | 8.5113* | 2.9719 | 0.004 | 2.6672 | 14.3553 |

*$p < 0.05$. Values compared using ANOVA and *post hoc* test.
1 = GA < 13 weeks; 2 = 12 weeks < GA < 21 weeks; 3 = 20 weeks < GA < 25 weeks; 4 = 24 weeks < GA < 29 weeks; 5 = 28 weeks < GA < 37 weeks; 6 = GA > 36 weeks. CI = confidence interval; GA = gestational age; SE = standard error.

The appetite of most pregnant women increases after the fourth month of gestation when symptoms of nausea and vomiting disappear.[17] Therefore, in addition to uterine content, systemic organs including subcutaneous adipose tissue, omentum, blood volume and breasts increase in size with advancing gestation. Leptin is one of the proteins produced by syncytiotrophoblasts in the placenta.[3,4] Theoretically, the amount of leptin synthesized by the placenta should increase due to the increased size of the placental mass with advancing gestation. However, Henson et al[7] have reported that leptin receptors in the placenta show no apparent changes and local leptin mRNA declines with increased GA. In the study of Yura et al,[18] leptin secretion from chorionic tissue in the first trimester was approximately 50-fold greater than that of term placental tissue. However, other than placenta and adipose tissue, leptin can be synthesized by mammary epithelial cells,[6] fetal tissue, gastric mucosa, and hepatic stellate cells.[5] With the additional increase in leptin in these organs, significant changes in serum leptin levels related to GA were found in the second trimester.

Serum leptin levels peaked early in the third trimester. This finding was in agreement with Tamas et al's study.[16] Tamas et al found no significant correlation between maternal serum leptin and GA in the third trimester. In the study of Schubring et al,[10] leptin levels peaked at term (38–40 weeks). The difference from our results was because parts of the gestational period were skipped when blood samples were collected. In our study, with advancing GA, maternal leptin levels decreased significantly in spite of a rapid increase in fetal weight during the third trimester. Meanwhile, maternal body weight ($p = 0.039$) and BMI ($p = 0.053$) were not related simultaneously to GA, since the effect of mobilization of maternal stored fat during earlier pregnancy could support the energy requirements of the rapidly growing fetus.[12] As a result, not only did maternal fat mass begin to decrease at this stage, but the secretion of leptin was also affected.

In conclusion, maternal serum leptin concentration throughout the pregnancy course correlates not only to body weight and BMI but also to GA. There is no significant relationship between maternal serum leptin and GA in the first trimester. Maternal serum leptin is correlated to GA in the second trimester but is inversely related to GA in the third trimester. The concentration of maternal serum leptin peaks in the early third trimester and declines significantly thereafter. Maternal BMI is related to GA in the second trimester and the whole pregnancy, but not in the first and third trimesters.

## Acknowledgments

The author would like to acknowledge Dr. Ren-Shyan Liu, Chief of the Department of Nuclear Medicine, for his full laboratory support, Ms. Tsong-Shir Yang for her provision of IRMA, and Stella YC Wu, PharmD, for reviewing this manuscript. The financial support from the project TVGH 890410-16 is also acknowledged.

## References

1. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994;372:425–32.
2. Van Harmelen V, Reynisdottir S, Eriksson P, Thorne A, Hoffstedt J, Lonnqvist F, Arner P. Leptin secretion from subcutaneous and visceral adipose tissue in women. *Diabetes* 1998;47:913–7.
3. Masuzaki H, Ogawa Y, Sagawa N, Hosoda K, Matsumoto T, Mise H, Nishimura H, et al. Nonadipose tissue production of leptin: leptin as a novel placenta-derived hormone in humans. *Nat Med* 1997;3:1029–33.
4. Senaris R, Garcia-Caballero T, Casabiell X, Gallego R, Castro R, Considine RV, Dieguez C, et al. Synthesis of leptin in human placenta. *Endocrinology* 1997;138:4501–4.
5. Marti A, Berraondo B, Martinez JA. Leptin: physiological actions. *J Physiol Biochem* 1999;55:43–9.
6. Smith-Kirwin SM, O'Connor DM, De Johnston J, Lancey ED, Hassink SG, Funanage VL. Leptin expression in human mammary epithelial cells and breast milk. *J Clin Endocrinol Metab* 1998;83:1810–3.
7. Henson MC, Swan KF, O'Neil JS. Expression of placental leptin and leptin receptor transcripts in early pregnancy and at term. *Obstet Gynecol* 1998;92:1020–8.
8. Harigaya A, Nagashima K, Nako Y, Morikawa A. Relationship between concentration of serum leptin and fetal growth. *J Clin Endocrinol Metab* 1997;82:3281–4.
9. Gòmez L, Carrascosa A, Yeste D, Potau N, Riqué S, Ruiz-Cuevas P, Almar J. Leptin values in placental cord blood of human newborns with normal intrauterine growth after 30–42 weeks of gestation. *Horm Res* 1995;51:10–4.
10. Schubring C, Englaro P, Siebler T, Blum WF, Demirakca T, Kratzsch J, Kiess W. Longitudinal analysis of maternal serum leptin levels during pregnancy, at birth and up to six weeks after birth: relation to body mass index, skinfolds, sex steroids and umbilical cord blood leptin levels. *Horm Res* 1998;50:276–83.
11. Sattar N, Greer IA, Pirwani I, Gibson J, Wallace AM. Leptin levels in pregnancy: marker for fat accumulation and mobilization? *Acta Obstet Gynecol Scand* 1998;77:278–83.
12. Sivan E, Whittaker PG, Sinha D, Homko CJ, Lin M, Reece EA, Boden G. Leptin in human pregnancy: the relationship with gestational hormones. *Am J Obstet Gynecol* 1998;179:1128–32.
13. Hardie L, Trayhurn P, Abramovich D, Fowler P. Circulating leptin in women: a longitudinal study in the menstrual cycle and during pregnancy. *Clin Endocrinol* 1997;47:101–6.
14. Coleman RA, Herrmann TS. Nutritional regulation of leptin in humans. *Diabetologia* 1999;42:639–46.
15. Miles LEM, Lipschitz DA, Bieber CP, Cook JD. Measurement of serum ferritin by a 2-site immunoradiometric assay. *Analyte Biochem* 1974;61:209–24.
16. Tamas P, Sulyok E, Szabol I, Vizer M, Ertl T, Rascher W, Blum WF. Changes of maternal serum leptin levels during pregnancy. *Gynecol Obstet Invest* 1998;46:169–71.
17. Lacroix R, Eason E, Melzack R. Nausea and vomiting during pregnancy: a prospective study of its frequency, intensity, and pattern of change. *Am J Obstet Gynecol* 2000;182:931–7.
18. Yura S, Sagawa N, Ogawa Y, Masuzaki H, Mise H, Matsumoto T, Ebihara K, et al. Augmentation of leptin synthesis and secretion through activation of protein kinases A and C in cultured human trophoblastic cells. *J Clin Endocrinol Metab* 1998;83:3609–14.